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Friday, September 06, 2000

Dockets Management Branch (HFA-305) Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, Maryland 20852

P436 00 SEP 19 A9:59

Re: Draft revised guidance entitled ``Q3A(R) Impurities in New Drug Substances.'' Fed. Reg. Vol. 65 No. 140, July 20, 2000.

Sir/Madam:

On behalf of the International Association of Innovative and Generic Manufacturers (IAGIM), I am submitting comments and objections on "Impurities in New Drug Substances " Docket No. 94D 0325, Fed. Reg. Vol. 65 No. 140, July 20, 2000.

IAGIM is comprised of manufactures and developers of generic and innovative drugs worldwide as well as the providers of technical services and drug development know-how to these firms and institutions. Many of our members will be directly impacted by implementation of the rounding-up paragraph in the proposed guideline, amending the agency's current regulations on "Impurities in New Drug Substances" with specific respect to the cost and identification parameters impacting on the eventual approved application.

IAGIM has long taken a leading role in advocating for harmonization of laws and regulations through its official publication The Int. J. of Generic Drugs, that assures the most expeditious availability of high-quality, low-cost generic and innovative drug development and end products to global drug consumers, not solely limited to the US and EU.

As these guidelines impact on the drug development costs, the cost of establishing an overall drug substances impurity profile, at all FDA approved global drug development sites (whether in the US, EU or ROW) will be significantly increased with no significant clinical or adverse effects benefit.

No logical scientific benefit or mathematical logic based on good scientific practice has been demonstrated by such a rounding definition which will impact negatively on the cost of developing the drug substances impurity profile as currently used in the drug development and generic know-how technology development units in the US, EU and Rest of the World where these drug development establishments are required to meet either the US and/or EU guidelines for harmonization, marketing or other purposes.

Thus, we are pleased to offer the following comments on the proposed regulations with respect to matters of rounding procedures.

OVERVIEW

While IAGIM recognizes the initial work and joint intellectual effort input by the US and EU agencies (via ICH) in developing these New Drug Substances impurity proposals, IAGIM is concerned that several elements of the proposal, place more significance on rounding-up and rounding–down procedures to the number **0.1%** of the labeled amount (which represents the identification threshold, namely the level at where impurity/degradant identification is required) than on the proper scientific interpretation of rounding impurity levels to the most significant figures as appropriate to the quantitation limit (QL) of the (said) HPLC or other instrument test method.

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As modern HPLC methodology can readily and routinely detect individual impurities to the second and third decimal places (namely 0.065% of labeled amount) and can accurately distinguish a difference between 0.050 and 0.075; It violates good scientific rounding procedures to regard these two accurate accessed impurity values, by agency regulation, as both equal to 0.1% by imposing an arbitrary rounding definition and then limiting the end value to only one decimal place.

In the best case scenario, the limit of impurities and degradants should be limited to two significant[1] decimal places with reference to the pivotal value of 0.1%, which is the recognized cut-off identification value and has attached to it an existing agency guideline definition requiring further development and identification (with the incorporated increased development and assay costs).

For this reason, and other specific reasons mentioned herein, IAGIM opposes the proposed definition and example of rounding as found in the proposed revised glossary namely;

Proposed Definition

> Rounding: The process of reducing a result to the number of significant figures or number of decimal places as dictated by the appropriate limit. For example, a result greater than or equal to (≥) 0.05 and less than (<) 0.15 is rounded to 0.1.

IAGIM offers the following definition to the glossary to clarify the regulations and improve the procedural practice of rounding up or down.

Amended Definition

> Rounding: The process of rounding a result to the number of significant figures or a number of appropriate decimal places. For example, a result in the range of 0.055 - 0.064 shall be rounded-up to 0.06 and a result in the range of 0.146 - 0.154 is rounded to 0.15...

Furthermore appropriate sections of the guideline text should be amended to meet all numerical situations where rounding may occur so as to standardize any impurity assay results so obtained to TWO significant decimals where the values have exceeded the Quantitation Limit (QL) capability for the assay of the instrument being used.

It must be clearly stated that good science dictates that rounding procedures are to be solely used for mathematical standardization and data clarity so that results can be simply understood by all concerned without compromising accuracy of individual results and furthermore it should not be used, as in the above rounding examples, to obtain an arbitrary percentage value. FDA's rounding procedures on the percentage of impurity assay values found between 0.050 to 0.095% are to be rounded as 0.1%, a value which the identification threshold has been reached requiring identifying the molecular impurity structure).

> Currently impurity structures should be identified when their percentage of the labeled amount is 0.1% or greater. The current procedures do not call for impurity or degradant identification of the molecular structure that has a HPLC peak count equivalent to 0.05, 0.06% or for that matter 0.09% of the labeled amount. The proposed guideline DOES NOT clarify if an impurity assay value should be initially adjusted to the 'rounded value' and THEN made subject to identification and qualification threshold.

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It appears, that under the proposed definition, that drug substances under 2000mg MDD, the future impurity structures (impurities and/or degradants) would be identified when their percentage of the labeled amount is 0.05% or greater, if the agencies new rounding-up definition were to be applied.

This procedure will in fact reduce by 50% the assay percentage level (Table 3) where impurities need to be identified and where their status change from 'unknown impurities' to 'known impurity structures', Although this draft revised guidance represents the agency's current thinking on impurities in new drug products, it does not create or confer any rights for or on any person and does not operate to bind FDA or the public. However the down-the-line impact on new drug development and subsequently generic equivalents, on patent expiry, will eventually be open the same arbitrary rounding procedures which may by default become the future industry standard for both the innovative and generic drug industry, thus increasing the overall cost of drug quality control.

The agency has not demonstrated with any appropriate supporting scientific database evidence that there is a need to reduce the assay peak count for impurity/degradation identification threshold from the currently 0.1% standard to a proposed 0.05% or less, as will be effected by the apparent arithmetic outcome of the proposed agency rounding procedure. Table 1 highlights new drug substances with a maximum daily dose of up to 4g per day, such as an existing example of (say) sucralfate 1g tablets.

Any equivalent new drug substances at this dosage level would require the assay limit for unknown impurities not to exceed 0.025% or 1 part in 4000. This is a significant departure from new drug substances with a MMD under 1 gram limiting unknown impurities to NMT 0.1% or 1 part in 1000.

Furthermore in this drug substance category the unknown impurities/degradants should not exceed 0.025% or 1 part in 4000 after stress testing at 40°C/75% RH for up to 6 months.
Commercial batch-to-batch variability as well as analytical variability will further bias these stringent limits and at times exceed the 0.025% limit thus creating an out-of-specification impurity assay and possibly lot rejection of the active drug substance batch, significantly increasing production costs.

TABLE 1.

New Drug Substance Category.	Maximum Daily Dose - MDD (mg)	Assay Limit for 'unknown impurities'	
		%	In parts
New Drug Substance 1	1000	0.10	1 : 1000
New Drug Substance 2	1200	0.08	1 : 1200
New Drug Substance 3	1400	0.07	1 : 1420
New Drug Substance 4	1600	0.06	1 :1660
New Drug Substance 5	1800	0.055	1 :1820
New Drug Substance 6	2000	0.05	1 :2000
New Drug Substance 7	2200	0.045	1 :2220
New Drug Substance 8	2500	0.04	1 :2500
New Drug Substance 9	3000	0.03	1 :3300
New Drug Substance 10	4000	0.025	1 :4000

Drug substance categories 1 - 6 as above (Table 1) would, under the new agency proposed "Impurities in New Drug Substances " guidance rounding rules, elevate any unknown impurity to the arbitrary "rounding level" of 0.1% thus requiring identification and qualification. Drug substance categories 7 - 9 (Table 1 as above) would require ALL unknown impurity to meet the reporting threshold, irrespective of peak size (area).

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The new guidance calls for any New Drug Substances in the 1000 - 2000 mg maximum daily dose category showing unknown impurities of 0.05% - 0.094% be rounded up to 0.1% thus meeting the requirements for the identification and qualification threshold. Where a New Drug Substances displays a unknown impurity of Imp. A at 0.045 % and on stability testing at 40°C/75% RH for 3 months changes to 0.05% or 0.055% (which may be simple analytical variation - a common routine occurrence) the Imp. A would be rounded to 0.1% and be thus subject to an identification and qualification threshold. In practice the batch would be forfeited and rejected - even though the impurity/degradant had no actual growth and remained essentially the same value at time of manufacture.

TABLE 2.

Common existing Drug Examples	Maximum Daily Dose - MDD (mg)	Assay Limit for unknown impurities	
	Published MDD	%	Parts
Sodium Valproate	1750	0.06	1 :1660
Fosfomycin	3000	0.03	1 :3300
5-aminosalicylic acid	2000 - 3000	0.03	1 :3300
Tranexamic acid	4500	0.024	1 :4160
Sucralfate	4000	0.025	1 :4000

In conclusion the agency has not shown any toxicological evidence, whether of a general or specific nature, based on drug impurity profile percentages vs. patient clinical benefits, by departing from the 0.1% rule, to warrant that such a significant assay reporting change, with long term cost implications is either reasonable, justifiable or in the public health interest.

TABLE 3.

Impurity Percentage	Rounded to Significant Figures	FDA and EU New Proposal
0.050 - 0.054	0.050	0.10
0.055 - 0.059	0.060	0.10
0.060 - 0.064	0.060	0.10
0.065 - 0.069	0.070	0.10
0.070 - 0.074	0.070	0.10
0.075 - 0.079	0.080	0.10
0.080 - 0.084	0.080	0.10
0.085 - 0.089	0.090	0.10
0.090 - 0.094	0.090	0.10
0.095 - 0.099	0.10	0.10

Key :

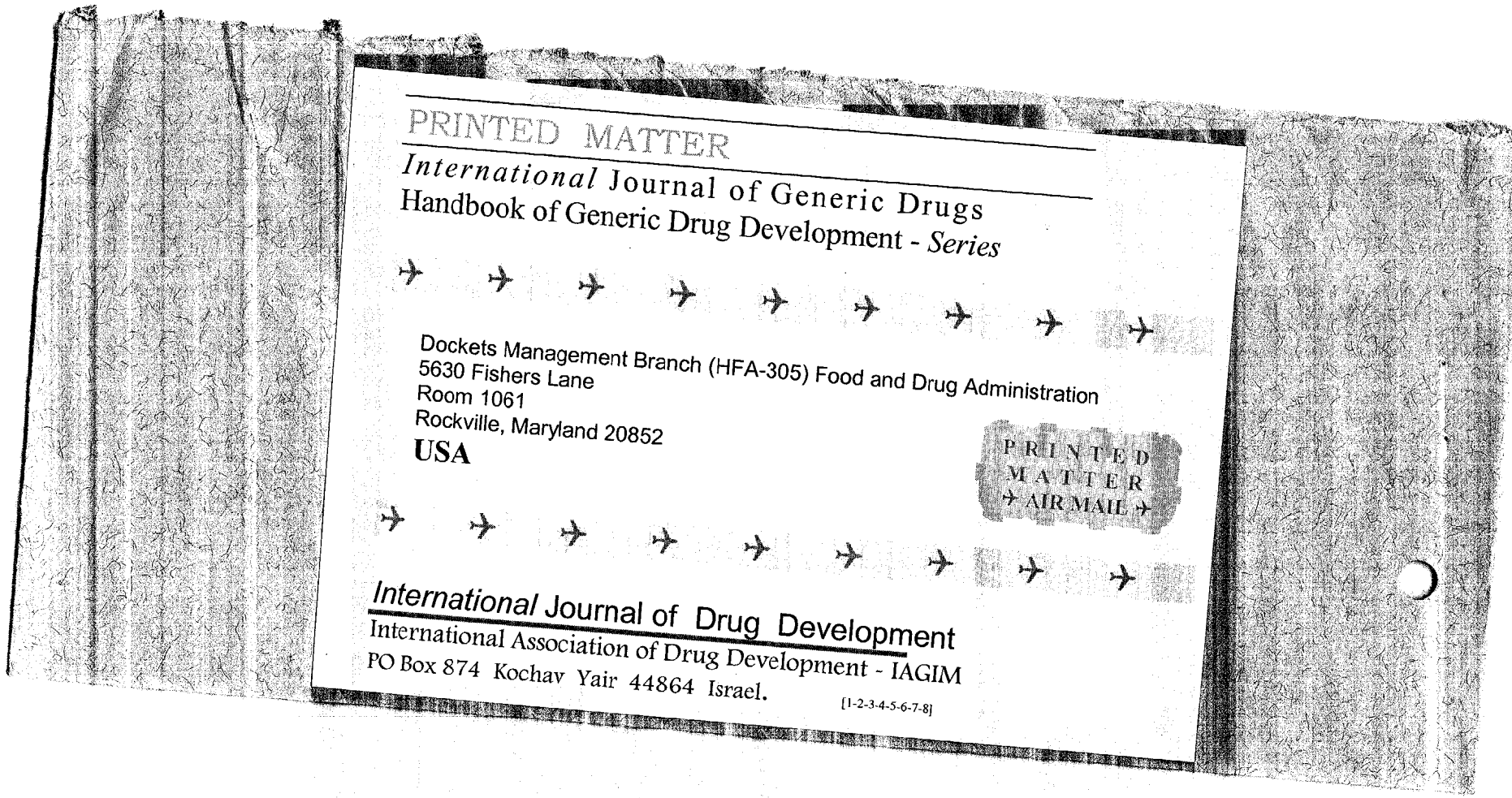
[1]SIGNIFICANCE	EXAMPLE	
One Significant decimal place	0,1[x]	1:1000
Two Significant decimal places	0.05[x]	1:2000
Three Significant decimal places	0.095[x]	1:1053

[x] = The value of this decimal imparts significance to the decimal on the immediate left of it. This is the mathematical meaning of SIGNIFICANCE. When this value is equal or greater than [x] = 5 only the decimal on the immediate left is rounded up, and the result is reported to one, two or three significant figures. Rounding can only occur once in a numerical set

Sincerely,

Jeremy. D. BLOCK
BSc, MPS, D. Pharm (Wits)
Senior Research Scientist.
IAGIM Scientific Review Committee.

[1] Impurities in New Drug Products Docket No. 94D 0325, FR. Vol. 65 No. 140, July 20, 2000.



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